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Long-Term Effectiveness and Safety of Sirolimus Stent Implantation for Coronary In-Stent Restenosis

Results of the TRUE (Tuscany Registry of Sirolimus for Unselected In-Stent Restenosis) Registry at 4 Years

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Objectives The aim of this study was to evaluate the long-term clinical outcome of the efficacy and safety of sirolimus-eluting stents (SES) for in-stent restenosis (ISR) in the TRUE (Tuscany Registry of Unselected In-Stent Restenosis) database.

Background The TRUE registry demonstrated that SES in the treatment of bare-metal stent ISR is efficacious (5% of target lesion revascularization [TLR]) and safe (stent thrombosis <1%) at 9 months. Clinical outcome at 4 years is reported.

Methods A total of 244 patients with ISR who were treated with SES implantation represent the study population. The incidence of major adverse cardiac events was collected at 4 years.

Results At 4-year follow-up, overall mortality was 9.8% (24 patients). Cardiac death occurred in 11 (4.5%), nonfatal myocardial infarction in 8 (3.2%), and TLR in 27 (11.1%) patients for a cumulative event-free survival rate of 80.3%. Definite stent thrombosis occurred in 5 (2%) patients and possible stent thrombosis in 2 (0.8%). Diabetes remained an independent negative predictor of freedom from TLR (odds ratio [OR]: 0.38; 95% confidence interval [CI]: 0.20 to 0.71, p = 0.002) and major adverse cardiac events (OR: 0.38; 95% CI: 0.20 to 0.71, p = 0.002).

Conclusions The clinical benefit of SES implantation for bare-metal stent ISR is maintained at 4 years with a low TLR rate and an overall incidence of stent thrombosis of 0.7% per year. (J Am Coll Cardiol 2010;55:613–6) © 2010 by the American College of Cardiology Foundation

The superiority of drug-eluting stents (DES) compared with balloon angioplasty and vascular brachytherapy for the treatment of patients with in-stent restenosis (ISR) has been shown in observational and randomized trials (1–4). However, because both DES and brachytherapy similarly share inhibition of late loss as the mechanism of benefit, a long-term follow-up is needed to show whether the benefit is diluted over years. Furthermore, the advent of DES has raised concerns regarding later occurrence of stent thrombosis beyond the traditional 9-month time frame (5–8), especially in complex lesion subsets, such as patients with ISR. No data are currently available on the safety/benefit profile of DES in this subset of patients at long-term follow-up. Thus, we sought to investigate whether the midterm clinical benefit of DES implantation for bare-metal stent (BMS) ISR observed in the TRUE (Tuscany Registry of Unselected In-Stent Restenosis) (9) database was maintained long-term (4 years).

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Methods

The design of the registry has been previously reported (9). Briefly, the study was designed as a prospective, single-arm, 2-center registry to evaluate clinical outcome after the implantation of a sirolimus-eluting stent (SES) for the treatment of ISR. Combined antiplatelet therapy with aspirin (at least 100 mg daily) and ticlopidine 500 mg daily (or clopidogrel 75 mg daily) was started at least 48 h before the procedure and continued for at least 6 months.

Study population and definitions. Two hundred forty-four consecutive patients treated with SES implantation

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
IDTLR = ischemia-driven target lesion revascularization
ISR = in-stent restenosis
MACE = major adverse cardiac events
OR = odds ratio
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization

for BMS restenosis were followed up until 4 years after study entry.

Bifurcation restenotic lesions were defined as a restenosis >50% in both the main branch and the ostium of the side branch. Major adverse cardiac events (MACE) were defined as death from any cause, nonfatal reinfarction, and ischemia-driven target lesion revascularization (IDTLR). Myocardial infarction was defined as the presence of new Q waves in ≥2 contiguous electrocardiogram leads or an elevation of creatine kinase or its myocardial band isoenzyme to ≥3 times the upper limit of normal in 2 samples during hospitalization or to 2 times the upper limit of normal after discharge. IDTLR was defined as any repeat revascularization due to lumen renarrowing within the stent or in the 5-mm distal or proximal segments associated with symptoms or objective signs of ischemia. Stent thrombosis (ST) was defined according to the Academic Research Consortium classification (10).

Statistical analysis. Values are reported as numbers with relative percentage or SD. Kaplan-Meier analysis was used to assess survival free from MACE and survival free from IDTLR alone. Cox regression analysis was used to identify independent predictors of MACE and IDTLR alone. Odds ratio (OR) and 95% confidence intervals (CIs) were reported with 2-tailed probability value. A value of $p < 0.05$ was considered statistically significant. All statistical computations were performed by StatView version 6 (SAS Institute, Cary, North Carolina) procedures.

Results

Baseline clinical and procedural variables of the patients were previously reported in detail (9). Twenty-three patients presented with a restenosis at the bifurcation site (distal left main in 3 patients, left anterior descending artery in 12 patients, circumflex in 8 patients) involving a BMS in the main branch while the ostium of the side branch was not primarily stented. All these bifurcation restenoses were treated with SES implantation in the main branch and a balloon dilation in the side branch.

Clinical outcome at 1 year, between 1 and 4 years follow-up, as well as for the entire study period is reported in the Table 1.

A follow-up period of 4 years was achieved in all patients. Beyond the 1-year time frame (Table 1), we observed 31 new MACE episodes: 20 additional patients died (7 from cancer, 2 from renal failure, 2 from stroke, 1 during surgical limb revascularization, 4 from heart failure, 1 perioperatively for coronary artery bypass graft, 2 from fatal infarction, 1 from sudden death), 4 patients had a nonfatal infarction, and 14 patients had IDTLR. Overall, during the entire study period, death occurred in 24 patients (10%) (31 ± 19 months from the procedure, mean age 73 ± 12 years). The cumulative incidence of MACE was 20% (48 events) and of TLR was 11% (Fig. 1). Cox regression model showed that diabetes (OR: 0.38; 95% CI: 0.20 to 0.71, p = 0.002), left ventricular ejection fraction <50% (OR: 0.32; 95% CI: 0.13 to 0.80, p = 0.01), and creatinine >1.5 mg/dl (OR: 0.23; 95% CI: 0.11 to 0.48, p = 0.0001) were independent predictors of MACE. Diabetes (OR: 0.32; 95% CI: 0.14 to 0.71, p = 0.005) and peripheral or carotid arterial disease (OR: 0.35; 95% CI: 0.14 to 0.88, p = 0.02) were independent predictors of IDTLR alone. In patients with diabetes, Kaplan-Meier estimation of freedom from MACE is reported in Figure 2 and IDTLR alone in Figure 3.

Definite ST occurred in 5 (2%) patients (at 261, 614, 621, 631, and 847 days from the index procedure), and it was fatal in 2 patients. Except for 1 patient who was on aspirin and clopidogrel at the time of the event, all patients interrupted clopidogrel more than 1 month before the event. There were 2 additional episodes of possible ST in 2 elderly patients (ages 85 and 89 years) treated for ISR of the left main at 60 and 538 days from the index procedure, both on aspirin and clopidogrel at the time of the event. Thus, the cumulative incidence of definite, probable, or possible ST during the all-study period was 2%, 0%, and 0.8% (Table 1). The mean duration of dual antiplatelet treatment (either clopidogrel or ticlopidine and aspirin) was 341 ± 112 days. It was continued for 6 months in 52 patients (21%), for 12 months in 168 patients (69%), and 24 months in 24 (10%) patients.

Table 1 Clinical Outcome at 4 Years

	1 Year	4 Years	Total
Death	4 (1.6)	20 (8.2)	24 (9.8)
Cardiac	3 (1.2)	8 (3.2)	11 (4.5)
Noncardiac	1 (0.4)	12 (4.9)	13 (5.3)
MI	5 (2)	6 (2.5)	11 (4.5)
Fatal	1 (0.4)	2 (0.8)	3 (1.2)
Nonfatal	4 (1.6)	4 (1.6)	8 (3.2)
Stent thrombosis	2 (0.8)	5 (2)	7 (2.8)
Definitive	1 (0.4)	4 (1.6)	5 (2)
Probable	0	0	0
Possible	1 (0.4)	1 (0.4)	2 (0.8)
IDTLR	13 (5.0)	14 (6.0)	27 (11.1)
PCI	12 (4.5)	11 (4.7)	23 (9.4)
CABG	1 (0.4)	3 (1.2)	4 (1.6)
Free from MACE	226 (93)	196 (80)	196 (80)

Data presented as n (%).
CABG = coronary artery bypass graft; IDTLR = ischemia-driven target lesion revascularization; MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

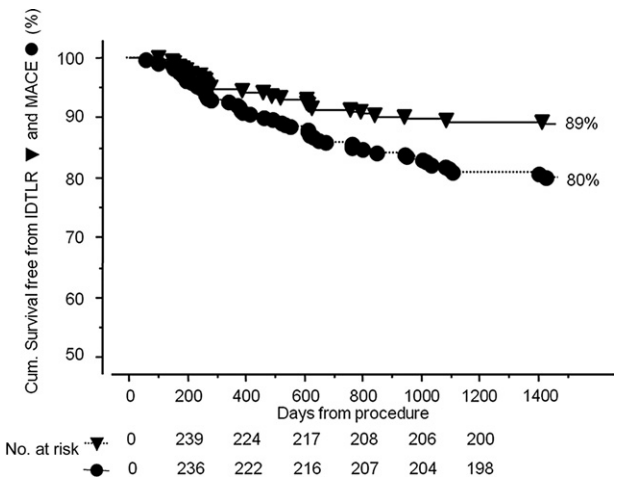

Figure 1 **Kaplan-Meier Survival Curves in the Whole Study Group**

Survival free from major adverse cardiac events (MACE) and ischemia-driven target lesion revascularization (IDTLR) at 4-year follow-up.

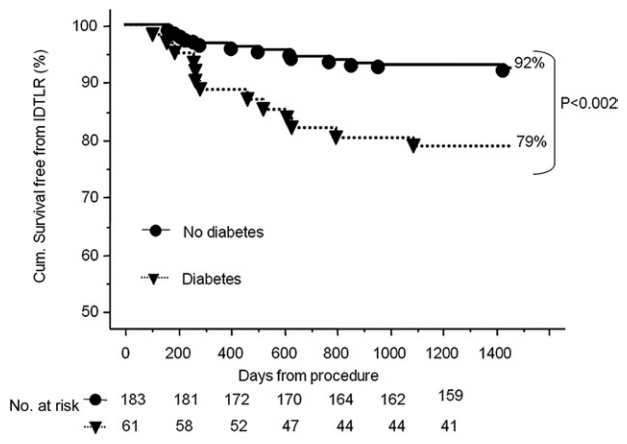

Figure 3 **Kaplan-Meier Survival Curves for IDTLR in Diabetic Population**

Survival free from IDTLR at 4-year follow-up in patients with and without diabetes. Abbreviation as in Figure 1.

Discussion

Several registries as well as randomized clinical trials have shown the superiority of DES over balloon angioplasty and vascular brachytherapy in the treatment of ISR (1–4). However, the majority of these studies showed efficacy and acceptable safety of DES over a limited follow-up period, and few data on long-term outcome are available. In addition, after the pivotal reports describing the occurrence of late ST after DES implantation, consistent findings have been echoed by several different groups (5,7,11), raising a note of caution regarding the safety/efficacy profile of this new coronary technology when employed in unselected patient/lesion subsets such as ISR. To our knowledge, this registry is the largest series of patients treated with SES for ISR lesions in a real-world scenario with no exclusion criteria concerning patients' clinical status as well as angiographic criteria and followed-up in a long-term format.

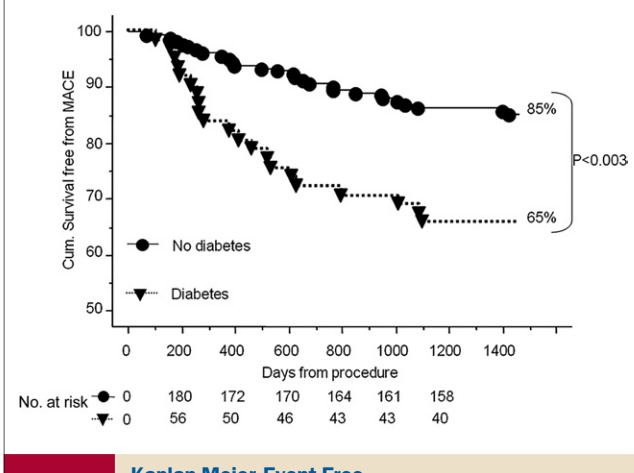

Figure 2 **Kaplan-Meier Event-Free Survival Curves in Diabetic Population**

Survival free from the combined end point of cardiac death, myocardial infarction, and IDTLR at 4-year follow-up in patients with and without diabetes. Abbreviations as in Figure 1.

Major findings of the study. 1) Clinical results at 4 years confirm the efficacy of SES in the prevention of IDTLR with an overall rate of 11% and the absence of late catch-up observed with brachytherapy or balloon angioplasty (12). Our results compare favorably with those reported in the DES arm of the SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) trial (4) (TLR 17% at 3 years) and TAXUS V ISR (Paclitaxel-Eluting Stents versus Brachytherapy for In-Stent Restenosis) trial (3) (TLR 10% at 2 years). However, the higher number of diabetic patients (33% in SISR, 40% in TAXUS V ISR vs. 26% in TRUE) and the different trial design (follow-up angiography in SISR) might explain the observed small differences in TLR rate. 2) We observed a cumulative incidence of ST of 2.8% (7 events; 0.70% per year) and a cumulative incidence of very late (>1 year) ST of 2% (5 events; 0.57% per year), as shown in other recent registries (6) and meta-analysis of the major randomized control trials related to DES implantation in de novo coronary lesion (11). However, the adverse prognostic influence of this event is also confirmed by our findings (50% mortality among patients exposed to the event), even if the 2 sudden deaths accounted as ST occurred in very elderly patients (age >85 years) and might be related to other causes. We did not find an excess of events after thienopyridine discontinuation because most ST episodes occurred several months after the drug cessation. 3) Finally, the higher rate of the combined end point of death, myocardial infarction, and IDTLR and IDTLR alone

observed at 9-month follow-up in patients with diabetes (9,13) was confirmed long term.

Study limitations. As a real-world registry, the study is inherently limited by a lack of valid control groups using historical controls. However, one should also recognize that many of the DES randomized trials performed for device approval have restricted enrollment criteria, making extrapolation of their findings to the greater population questionable (13).

The absence of a systematic late (>12 months) control coronary angiography did not allow a real estimation of the late catch-up phenomenon with DES in ISR lesions, which, however, seems to be clinically irrelevant. Finally, in patients with late occurrence of TLR, we could not exclude that the stenotic lesion inside the stented segment represented a new atherosclerotic lesion instead of a restenosis.

Conclusions

The midterm clinical benefit of SES implantation for BMS ISR is maintained over a long-term follow-up with a low TLR rate and an overall incidence of ST <1% per year.

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Key Words: sirolimus-eluting stent ■ in-stent restenosis ■ long-term clinical outcome ■ late stent thrombosis.